Molecular Cancer Research **Highlights**

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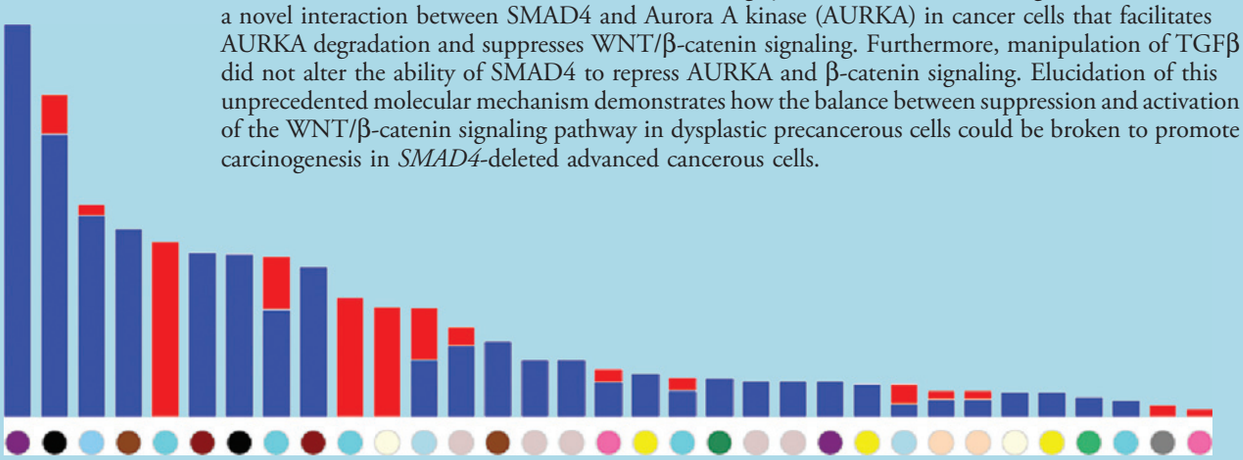
SMAD4 Suppresses AURKA Independent of TGFβ

Jia *et al.* **Page 1779**

Although SMAD4 has been suggested to inhibit the activity of the WNT/β-catenin signaling cascade in cancer, the mechanism of this inhibition remains largely unknown. Jia and colleagues have discovered a novel interaction between SMAD4 and Aurora A kinase (AURKA) in cancer cells that facilitates AURKA degradation and suppresses WNT/β-catenin signaling. Furthermore, manipulation of TGFβ did not alter the ability of SMAD4 to repress AURKA and β-catenin signaling. Elucidation of this unprecedented molecular mechanism demonstrates how the balance between suppression and activation of the WNT/β-catenin signaling pathway in dysplastic precancerous cells could be broken to promote carcinogenesis in *SMAD4*-deleted advanced cancerous cells.



ETV6–RUNX1 Inhibits CXCL12-Driven Cell Migration

Palmi *et al.* **Page 1796**

The ETV6–RUNX1 genomic fusion is a frequent initiating event in childhood leukemia; however, its role in leukemogenesis is only partly understood. Here, Palmi and colleagues show defective adhesion and migration properties in ETV6–RUNX1-positive B-cell progenitors (BCP). In particular, alterations in the expression of adhesion molecules impaired chemotactic response to the chemokine SDF1 (CXCL12) and a block in the GTPase CDC42 signaling pathway are described. The molecular details revealed in this study posit an altered interaction of ETV6–RUNX1-positive BCP with the microenvironment and represent initiating events in the evolution of the disease, from its preleukemic phase to clinical onset, with potential implications to develop strategies for effective leukemia eradication.

AGR2 as a Therapeutic Target in Breast Cancer

Wright *et al.* **Page 1829**

Most breast cancers are estrogen receptor (ER) positive and many exhibit intrinsic or acquired resistance to commonly used endocrine therapies. Wright and colleagues demonstrate that the proto-oncogene AGR2 is required for the viability of tamoxifen-sensitive and -resistant ERα-positive breast cancer cells and highlight the therapeutic utility, *in vitro* and *in vivo*, of interfering with the production and/or activity of this secreted protein. Further, a new regulatory pathway is defined wherein ligand activated ERα facilitates AGR2 expression, which is required for the maintenance of ERα expression. Surprisingly, AGR2 expression was shown to occur in an ERα-independent manner in tamoxifen-resistant breast cancer cells, an activity that was attributed to dysregulated signaling by the transcription factor FOXA1.

Adenosine Inhibits Invasion via Nonreceptor Mechanisms

Virtanen *et al.* **Page 1863**

Extracellular adenosine mediates diverse anti-inflammatory, angiogenic, tumor-promoting, and other signaling effects through activation of G-protein–coupled adenosine receptors. Along with "classical" receptor-mediated pathways, adenosine also exerts cytotoxic and other biologic effects through intrinsic mechanisms. Virtanen and colleagues establish that pretreatment of either human prostate or breast cancer cells with low concentrations of adenosine markedly inhibits cell invasion and migration capacity. Molecularly, these inhibitory effects involve cellular uptake of nucleosides, their intracellular interconversion into ADP/ATP, and eventually, the inhibition of phospho-AMPK1α and other signaling pathways. This study provides novel insight into the ability of adenosine to prevent tumor invasion via two different adenosine receptor-dependent and -independent mechanisms.

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